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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,824	06/25/2001	Eric Perrier	11123.24US01	9749

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EXAMINER
WEBER, JON P

ART UNIT	PAPER NUMBER
1651	10

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/888,824	PERRIER ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *25-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,4,5,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of the Claims

Claims 1-43 have been presented for examination.

Election/Restrictions

Applicant's election of Group I, claims 1-24 in Paper No. 9, filed 25 October 2002 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, only urging that they did not want to be bound by the logic of the Examiner, the election has been treated as an election effectively **without** traverse (MPEP § 818.03(a)). Claims 25-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. It is suggested that the nonelected claims be canceled in response to this Office action to expedite prosecution.

Claim Rejections - 35 USC § 112

Claims 4-5 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites "lipoprotein" at line 1, which lacks antecedent basis. It is thought that this should recite lipoprotein lipase.

Claim 5 recites "comprises or is essentially constituted of" which is confusing because these are two different standards of transitional language, interpreting "essentially constituted of" as "consisting essentially of". The metes and bounds cannot be clearly ascertained.

Claim 12 is confusing and contradictory because step (a) has the lipase incubated with the potentially active substance, while step (c) allows for the lipase to not be incubated with the potentially active substance.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for testing in the presence and absence of putative inhibitor, does not reasonably provide enablement for comparing a putative inhibitor to a known inhibitor as reference. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

It is not possible to determine the inhibitory nature of a putative compound solely on the basis of comparison to a known inhibitor. There are three possible outcomes from such a comparison: 1) $U < K$; 2) $U = K$; and 3) $U > K$, where U = activity in presence of unknown, and K = activity in presence of known inhibitor. In the first two cases, 1 and 2, it is clear that a determination of inhibition is possible because U either has more inhibitory or the same inhibitory activity as K. In case 3, all one knows is that with U there is more activity than K. One must compare to an absolute reference value, i.e., the absence of inhibitor to be able to interpret such a result. But this is exactly the same as testing in the presence and absence of inhibitor.

Hence, simple reference comparison to a known inhibitor cannot definitively identify that a compound will be an inhibitor active in the field of lipolysis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 4-5, 7-13 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Cook et al. (US 5,855,917).

Cook et al. (US 5,855,917) disclose inhibiting lipoprotein lipase with 20-carbon conjugated unsaturated fatty acids for the purpose of controlling body fat and/or body weight in animals. Example 3 and Table 1 establish that the activity of lipoprotein lipase was measured in the presence of and absence of the putative inhibitors. The assay was performed with 3T3-L1 (an ATCC cell line from mouse) preadipocytes. The putative inhibitors were combined with albumin for incubation with the heparin released lipoprotein lipase.

Claims 1-2, 4-5, 7-13 and 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Wagle et al. (US 6,326,396).

Wagle et al. (US 6,326,396) disclose testing for inhibition of lipoprotein lipase (from 3T3-L1 mouse cells?) with a eudesmanolide in example 8 and Table 3. Several concentrations of glycerol stabilized triolein substrate were used in the presence and absence of the test substance. The compound failed to significantly inhibit the enzyme.

Claims 1-2, 4-5, 7-13 and 22-24 are rejected under 35 U.S.C. 102(b) or (e) as being anticipated by Takahashi et al. (US 5,955,072) or equivalent Takahashi et al. (US 6,307,038); only the '072 citation will be referenced for convenience.

Takahashi et al. (US 5,955,072) disclose a method for determining inhibitory activity against lipoprotein lipase at Example M (begins at column 38, line 45). The assay involves measuring the lipoprotein lipase activity in the presence and absence of the test compound. The enzyme is from 3T3-L1 mouse cells. Glycerol stabilized triolein is used as substrate. Detection of products by scintillation counting.

Claims 1, 4-13 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeda et al. (US 5,244,798).

Takeda et al. (US 5,244,798) disclose that lipoprotein lipase from *Streptomyces* species is inhibited 30-40% by 1 mM Zn^{2+}, Fe^{3+}, and Mg^{2+}; 40% by 3 M NaCl; 40% by 10 mM deoxycoholate; and 30% by 400 μg/ml protamine sulfate (column 3, lines 44-49). A percent inhibition implies that comparison was made to the absence of the inhibitor; the assay is described in detail at column 4, lines 1-51 and comprising measuring fatty acid production. A range of different triglyceride substrates were tested (Table 1). BSA is added to the substrate

solution. The assay also comprises an enzymatic determination of the released glycerol to form a colored solution whose absorbance can be read at 545 nm (column 9, lines 1-40).

Claims 1-13 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Vainio et al. (1982).

Vainio et al. (1982) disclose that benzene boronic acid inhibits lipoprotein lipase catalyzed hydrolysis of triacylglycerols. The presence of ApoCII, an activator of the lipase, partly reverses the inhibition. The lipoprotein lipase was obtained from bovine milk; Apo CII was isolated from human VLDL. BSA is added as stabilizer to the triolein substrate.

Claims 1, 4-13 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (1990).

Cheng et al. (1990) disclose that ApoCII C-terminal peptides act as both an activator and an inhibitor of lipoprotein lipase (bovine milk). Dioleoyl-PC stabilized triolein was substrate in the presence of BSA. Control with no added ApoCII peptides was the reference.

Claims 1, 3-13 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Carroll et al. (1992).

Carroll et al. (1992) disclose that myocardial lipoprotein lipase (rat) is inhibited by U-57,908 (aka RHC 80267) compared to reference control with no compound. The assay has added albumin and ApoCII added to the triolein substrate.

Claims 1, 3-13 and 22-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Bensadoun et al. (1974).

Bensadoun et al. (1974) disclose inhibition of lipoprotein lipase from pig by 1M NaCl (Table 1). The assay comprises added albumin and pig serum to the radioactive triolein substrate. The serum contained an unknown activator (now known to be ApoCII). It was found that ApoLp-Glu could substitute for serum as activator.

N.B. Harsanyi et al. (US 5,162,359) is representative of a number or references that state that Triton WR-1339 inhibits lipoprotein lipase but do not present an assay procedure or data. Similarly, Park et al. (US 5,880,095) states that human Apo-CIII inhibits the activity of lipoprotein lipase but do not provide an assay procedure or data.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al. (US 5,855,917), Wagle et al. (US 6,326,396), Takahashi et al. (US 5,955,072), Takeda et al. (US 5,244,798), Vainio et al. (1982), Cheng et al. (1990), Carroll et al. (1992) and Bensadoun et al. (1974) in view of NEFA-C kit from Wako.

The teachings of Cook et al. (US 5,855,917), Wagle et al. (US 6,326,396), Takahashi et al. (US 5,955,072), Takeda et al. (US 5,244,798), Vainio et al. (1982), Cheng et al. (1990), Carroll et al. (1992) and Bensadoun et al. (1974) have been discussed above. Cook et al. (US 5,855,917), Wagle et al. (US 6,326,396), Takahashi et al. (US 5,955,072), Takeda et al. (US 5,244,798), Vainio et al. (1982), Cheng et al. (1990), Carroll et al. (1992) and Bensadoun et al. (1974) lack determining nonesterified fatty acids released by a colorimetric method or the specific extracts to assay.

NEFA-C kit from Wako is disclosed in the specification at page 10 to be a commercially available kit for measuring nonesterified fatty acids colorimetrically.

A person of ordinary skill in the art at the time the invention was made would have been motivated to substitute the NEFA-C kit from Wako to measure released nonesterified fatty acids colorimetrically for the generally radioactive measurements of Cook et al. (US 5,855,917), Wagle et al. (US 6,326,396), Takahashi et al. (US 5,955,072), Takeda et al. (US 5,244,798), Vainio et al. (1982), Cheng et al. (1990), Carroll et al. (1992) and Bensadoun et al. (1974) because of the well known advantages of colorimetry over radioactive measurements in terms of safety, cost and speed (ease of use).

The selection of the substance or extract to assay for lipoprotein lipase inhibitory activity is an arbitrary matter of experimental design choice. The fundamental assay as set forth in claims 1-16 do not require any particular source of sample to be tested, and for good reason, it doesn't matter to the screening assay claimed therein. Hence, the selection of one plant or another to screen does not materially change the assay steps at all. The steps remain the same, just the unknown being tested changes. There may be reasons for selecting a particular sample for

screening based on prior knowledge of potentially suitable agents being contained therein, but the actual screen steps are unchanged.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the NEFA-C kit from Wako to measure released nonesterified fatty acids colorimetrically for the generally radioactive measurements in the lipoprotein lipase assay of Cook et al. (US 5,855,917), Wagle et al. (US 6,326,396), Takahashi et al. (US 5,955,072), Takeda et al. (US 5,244,798), Vainio et al. (1982), Cheng et al. (1990), Carroll et al. (1992) and Bensadoun et al. (1974).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
January 8, 2003